Understanding the impact of IFNγR clustering on immune response pathways

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***Short Abstract* — Interferon-γ plays an important role in macrophage activation during the early steps of innate immunity. Propagation of immune response via INFγ is dependent on the spatial localization of the INFγR. EM images have found INFγR to be colocalized in caveolar membrane domains; whether this enhances or restricts signal remains to be elucidated, However, in an interesting twist, experimental evidence points to INFγ as a negative regulator of caveolin-1. In order to understand the spatial-temporal dynamics of INFγR membrane localization and further investigate the impact of IFNγR activation on gene and metabolic pathways that regulate caveolin-1 production we developed a simulation-based model using a coupled CSNSA-BioXyce platform that combines a spatial Monte Carlo method (CSNSA) with a circuit-based intracellular network simulator (BioXyce). In this work we explore the impact of receptor spatial organization on immune effector mechanisms and to complete the circle, the impact of IFNγ mediated effectors on spatial organization.**

***Keywords* — Spatial organization, gene networks, INFγR, caveolin-1, spatial modeling**

I. Purpose

Interferon-γ induces direct antimicrobial mechanisms and up-regulates antigen processing and presentation pathways (9). Interferon-γ activates these immune responses via the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway. The initial signaling events of IFNγ receptor (IFNγR) are often the rate limiting step and dependent on the spatial distribution of the IFNγ receptors (3).

Electron microscopy using immunogold labeled particles has revealed aggregation of IFNγR in membrane domains (1). With low numbers of receptors (10^2 to 10^3 receptors per cell (1)) spanning large distances (20um T cell and macrophage (3)) aggregation and colocalization are necessary mechanisms in the signal transduction pathway. Although the cell membrane is a vastly complex structure filled with heterogeneous microdomains IFNγR has been observed to colocalize in caveolar membrane domains (1, 2, 4, 5).

Experimental evidence shows the link between IFNγ and caveolar domains goes beyond spatial organization on the plasma membrane, gene networks of caveolin-1 and IFNγ seem to be entwined. Stimulating macrophages with IFNγ had an inhibitory effect on caveolin-1, the marker protein of caveola (7). In addition when transfecting cell lines HT20 and DLD1with caveolin-1 cDNA there is downregulation in iNos(6), a metabolic product of INFγ immune response. A complex regulatory network exists between caveolin-1, INFγ, and iNos.

This distinct network has yet to be fully elucidated. Starting with a model of the INFγ immune response (8) we have added gene networks of caveolin-1 as well as gene and metabolic networks of iNOS. In this study our aim is to understand the effects that spatial clustering has on IFNγR downstream signaling using the coupled spatial non-spatial simulation algorithm (CSNSA) to simulate the IFNγ/IFNγR mediated activation of the JAK-STAT signal transduction cascade. We then investigate the relationship between iNOS and caveolin-1 using a modeling framework which combines the CSNSA with BioXyce, where BioXyce is used to simulate the STAT mediated intracellular reactions that lead to the production of IFNγ activated genes and the metabolic reactions that lead to the production of immune effector molecules. We discuss the challenges and benefits of the coupled platform in providing a multiscale understanding of host immune response mechanisms.

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